MARK-UP OF AUTHORIZED CLAIMS

Claim 1 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; ~~and~~

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; and ~~thereby making said chimeric mouse~~

c. infecting the xenogenic mammalian hepatocytes with said one or more compatible hepatitis virus, said one or more compatible hepatitis virus selected from the group consisting of mammalian hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus,

thereby making said chimeric mouse.

Claim 2 (Currently amended): The method of claim 1, ~~further comprising~~ which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

Claim 3 (Currently amended): The method of claim 1, ~~further comprising~~ which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

Claim 4 (Previously presented): The method of claim 1, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 5 (Currently amended): The method of claim 4 [[1]], wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is human hepatitis B virus ~~at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus~~.

Claim 6 (Original):

The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

Claim 7 (Currently amended): The method of claim 6, wherein the xenogenic mammalian hepatocytes [[is]] are from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 8 (Currently amended): A chimeric mouse model system for hepatitis comprising:

an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said

immunetolerant mouse, and said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one [[a]] compatible mammalian hepatitis virus, and

said at least one compatible mammalian hepatitis virus is selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus.

Claim 9 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

Claim 10 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

Claim 11 (Currently amended): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes [[is]] are ~~a member~~ selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 12 (Currently amended): The chimeric mouse model system of claim 11 [[8]], wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is hepatitis B virus ~~at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus~~.

Claim 13 (Previously presented): The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

Claim 14 (Original): The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 15 (Currently amended):

A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus; and

b. assaying the level of replication of the virus;

thereby screening said test compound for anti-viral activity.

Claim 16 (Currently amended): The method of claim 15, wherein the mammalian hepatitis virus is hepatitis B ~~at least one hepatitis~~ virus.

Claim 17 (Original): The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

Claim 18 (Currently amended): The method of claim 15, ~~which comprises~~ ~~infecting~~ wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus prior to said transplanting.

Claim 19 (Currently amended): The method of claim 16, ~~which comprises~~ ~~infecting~~ wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus following said repopulating step.

Claims 20 (Currently amended): The method of claim 15, which comprises selecting the xenogenic mammalian hepatocytes from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 21 (Currently amended): The method of claim 20 [[15]], wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian virus is hepatitis B virus ~~at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus~~.

Claim 22 (Previously presented): The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

Claim 23 (Original): The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 24 (Original): The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Claim 25 (Currently amended):

A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells,

said mice having a ~~which have~~ degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice,

said degenerated liver parenchyma being ~~that is~~ repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes,

where said at least one compatible mammalian hepatitis virus is selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus; ~~and~~

b. assaying said mice for the development of hepatocellular carcinoma virus; and

c. comparing the assay in the chimeric mice with the same assay carried out in control mice which have not been administered the test compound,

wherein the chimeric mice have precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue,

thereby screening said test compound for anti-cancer activity.

Claim 26 (Currently amended): The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the livers of said ~~mouse~~ mice and in [[a]] control ~~mouse~~ mice which [[has]] have not been administered the test compound.

Claim 27 (Cancelled)

Claim 28 (Cancelled)

Claim 29 (Currently amended): The method of claim 25, ~~which comprises~~ ~~infecting~~ wherein the xenogenic mammalian hepatocytes were infected with a hepatitis virus prior to said transplantation step.

Claim 30 (Cancelled)

Claim 31 (Currently amended): The method of claim 25, ~~which comprises~~ ~~infecting~~ wherein the xenogenic mammalian hepatocytes ~~are~~ were infected with hepatitis virus following said repopulating step.

Claim 32 (Currently amended): The method of claim 25, ~~which comprises~~ ~~selecting~~ wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

Claim 33 (Currently amended): The method of claim 32 [[25]], wherein the xenogenic mammalian hepatocytes are human hepatocytes and the compatible mammalian hepatitis virus is hepatitis B virus ~~at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus~~.

Claim 34 (Currently amended): The method of claim 25, wherein the immunetolerant ~~mouse~~ mice which [[has]] have a degenerated liver [[is]] are hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

Claim 35 (Original): The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 36 (Original): The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Claim 37 (Cancelled)

Claim 38 (Cancelled)

Claim 39 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; ~~and~~

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver; and ~~thereby making said chimeric mouse~~

c. infecting said hepatocytes with one or more compatible hepatitis virus selected from the group consisting of hepatitis A virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus and hepadnavirus,

thereby making said chimeric mouse.

Claim 40 (Previously presented): The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

Claim 41 (Previously presented): The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

Claim 42 (Previously presented): The method of claim 1 wherein said uPA gene encodes secreted uPA.

Claim 43 (Previously presented): The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

Claim 44 (Previously presented): The method of claim 15 wherein said uPA gene encodes secreted uPA.

Claim 45 (Previously presented): The method of claim 25 wherein said uPA gene encodes secreted uPA.

Claim 46 (Cancelled)

Claim 47 (Cancelled)

Claim 48 (Previously presented): The method of claim 39 wherein said uPA gene encodes secreted uPA.

Claim 49 (New): The method of claim 39, which comprises infecting said hepatocytes with hepatitis virus prior to said transplanting.

Claim 50 (New): The method of claim 39, which comprises infecting said hepatocytes with hepatitis virus following said repopulation.

Claim 51 (New): The method of claim 39, which comprises infecting said hepatocytes with hepatitis B virus.

Claim 52 (New) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration;

b. repopulating the parenchyma of the degenerated liver by transplanting human hepatocytes into said liver; and

c. infecting said human hepatocytes with human hepatitis B virus,

thereby making said chimeric mouse.

Claim 53 (New): A chimeric mouse model system for hepatitis comprising:

an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and said degenerated liver being repopulated with transplanted human hepatocytes that are infected with human hepatitis B virus.

REMARKS

The present paper confirms the substance of the Examiner's Amendment authorized on March 19, 2004.

I. Examiner Interviews. The undersigned agent conducted telephonic interviews with Examiner Paras of the USPTO on March 11, 2004 and March 18, 2004, to discuss the pending claims in the application. During the latter interview, agreement was reached on allowable claims. The undersigned agent expresses his appreciation to the Examiner for the courtesies extended during the aforementioned interviews.

II. Amendments to the Claims. Applicant authorized that claims 1, 2, 3, 5, 7, 8, 11, 12, 15, 16, 18, 19, 20, 21, 25, 26, 29, 31, 32, 33, 34 and 39 be amended.

Claims 27, 28, 30, 37, 38, 46 and 47 were authorized to be cancelled, without prejudice or disclaimer.

Applicant authorized that new claims 49-53 be added.

Support for the amended and new claims is found in the following places in the application as filed:

Claims 1, 8, 15, and 39: Specification at page 9, lines 25-32.

Claim 25: Specification at page 9, lines 25-32 and original claims 27 and 28.

Claims 2, 3, 7, 11, 18, 19, 20, 26, 29, 31, 32 and 34: The changes to these claims are editorial in nature. Accordingly, no new matter is added to the application by these changes.

Claims 5, 12, 16, 21, 33, 51, 52 and 53: Specification at page 9, lines 15-19 and 35, and Example 14, page 29 et seq.

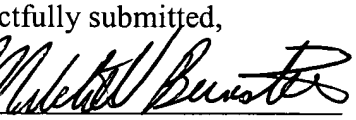
Claims 49 and 50: Specification at page 8, lines 5-7.

All amendments and the new claims are supported by the application as filed. Accordingly, by this Amendment, no new matter has been added to the application.

III. Examiner's Amendment. On March 19, 2004, Applicant authorized the Examiner to enter an Examiner's Amendment amending the claims to adopt the agreement reached with the Examiner. The Examiner was authorized to enter the claims set forth above.

Alternatively, the Examiner was authorized to cancel all existing claims in the application and enter new claims reflecting the claims set forth above, at his discretion.

Respectfully submitted,

By 

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